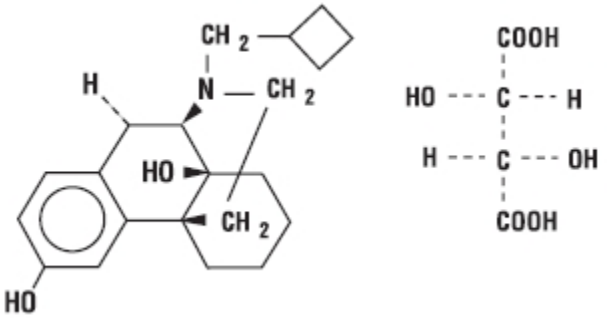
BUTORPHANOL TARTRATE - butorphanol tartrate spray
Mylan Pharmaceuticals Inc.

DESCRIPTION

Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(cyclobutylmethyl) morphinan-3, 14-diol [S-(R*,R*)] –2,3 – dihydroxybutanedioate (1:1) (salt). The molecular formula is $C_{21}H_{29}NO_2 \cdot C_4H_6O_6$, which corresponds to a molecular weight of 477.55 and the following structural formula:



Butorphanol tartrate is a white crystalline substance. The dose is expressed as the tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.
Butorphanol Tartrate Nasal Solution, USP is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. Each mL contains 10 mg of butorphanol tartrate, 6.5 mg sodium chloride, 1 mg citric acid, 1.2 mg sodium hydroxide, 0.2 mg benzethonium chloride in purified water; pH adjusted to 5.0 with sodium hydroxide and/or hydrochloric acid, if necessary. The pump reservoir must be fully primed (see PATIENT INSTRUCTIONS) prior to initial use. After initial priming each metered spray delivers an average of 1 mg of butorphanol tartrate and the 2.5 mL bottle will deliver an average of 14 to 15 doses of Butorphanol Tartrate Nasal Solution. If not used for 48 hours or longer, the unit must be reprimed (see PATIENT INSTRUCTIONS). With intermittent use requiring repriming before each dose, the 2.5 mL bottle will deliver an average of 8 to 10 doses of Butorphanol Tartrate Nasal Solution depending on how much repriming is necessary.

CLINICAL PHARMACOLOGY

General Pharmacology and Mechanism of Action

Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the μ-opioid type (morphine-like). It is also an agonist at κ-opioid receptors.
Its interactions with these receptors in the central nervous system apparently mediate most of its pharmacologic effects, including analgesia.
In addition to analgesia, CNS effects include depression of spontaneous respiratory activity and cough, stimulation of the emetic center, miosis, and sedation. Effects possibly mediated by non-CNS mechanisms include alteration in cardiovascular resistance and capacitance, bronchomotor tone, gastrointestinal secretory and motor activity, and bladder sphincter activity.
In an animal model, the dose of butorphanol tartrate required to antagonize morphine analgesia by 50% was similar to that for nalorphine, less than that for pentazocine and more than that for naloxone.
The pharmacological activity of butorphanol metabolites has not been studied in humans; in animal studies, butorphanol metabolites have demonstrated some analgesic activity.
In human studies of butorphanol (see Clinical Trials), sedation is commonly noted at doses of 0.5 mg or more. Narcosis is produced by 10 to 12 mg doses of butorphanol administered over 10 to 15 minutes intravenously.
Butorphanol, like other mixed agonist-antagonists with a high affinity for the κ-receptor, may produce unpleasant psychotomimetic effects in some individuals.
Nausea and/or vomiting may be produced by doses of 1 mg or more administered by any route.
In human studies involving individuals without significant respiratory dysfunction,2 mg of butorphanol IV and 10 mg of morphine sulfate IV depressed respiration to a comparable degree. At higher doses, the magnitude of respiratory depression with butorphanol is not appreciably increased; however, the duration of respiratory depression is longer. Respiratory depression noted after administration of butorphanol to humans by any route is reversed by treatment with naloxone, a specific opioid antagonist (see OVERDOSAGE: Treatment).
Butorphanol tartrate demonstrates antitussive effects in animals at doses less than those required for analgesia.
Hemodynamic changes noted during cardiac catheterization in patients receiving single 0.025 mg/kg intravenous doses of butorphanol have included increases in pulmonary artery pressure, wedge pressure and vascular resistance, increases in left ventricular end diastolic pressure, and in systemic arterial pressure.

Pharmacodynamics

The analgesic effect of butorphanol is influenced by the route of administration. Onset of analgesia is within a few minutes for intravenous administration, within 15 minutes for intramuscular injection, and within 15 minutes for the nasal solution doses.

Peak analgesic activity occurs within 30 to 60 minutes following intravenous and intramuscular administration and within 1 to 2 hours following the nasal spray administration.

The duration of analgesia varies depending on the pain model as well as the route of administration, but is generally 3 to 4 hours with IM and IV doses as defined by the time 50% of patients required remedication. In postoperative studies, the duration of analgesia with IV or IM butorphanol was similar to morphine, meperidine, and pentazocine when administered in the same fashion at equipotent doses (see Clinical Trials). Compared to the injectable form and other drugs in this class, butorphanol tartrate nasal solution has a longer duration of action (4 to 5 hours) (see Clinical Trials).

Pharmacokinetics

After nasal administration, mean peak blood levels of 0.9 to 1.04 ng/mL occur at 30 to 60 minutes after a 1 mg dose (see Table 1).

The absolute bioavailability of butorphanol tartrate nasal solution is 60% to 70% and is unchanged in patients with allergic rhinitis.

In patients using a nasal vasoconstrictor (oxymetazoline), the fraction of the dose absorbed was unchanged, but the rate of absorption was slowed. The peak plasma concentrations were approximately half those achieved in the absence of the vasoconstrictor.

Following its initial absorption/distribution phase, the single dose pharmacokinetics of butorphanol by the intravenous, intramuscular, and nasal routes of administration are similar (see Figure 1).

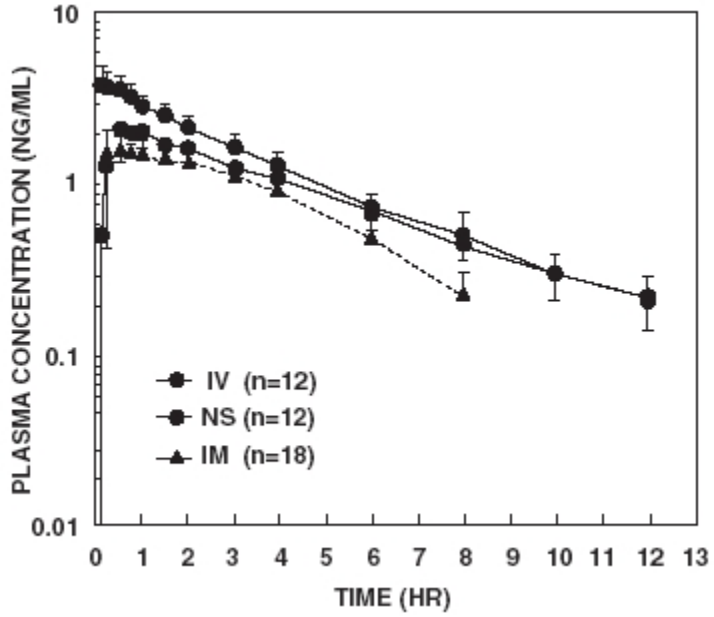


Figure 1 Butorphanol Plasma Levels After IV, IM, and Nasal Solution Administration of 2 mg Dose

Serum protein binding is independent of concentration over the range achieved in clinical practice (up to 7 ng/mL) with a bound fraction of approximately 80%.

The volume of distribution of butorphanol varies from 305 to 901 liters and total body clearance from 52 to 154 liters/hour (see Table 1).

Table 1 Mean Pharmacokinetic Parameters of Butorphanol in Young and Elderly Subjects*

	Intravenous		Nasal	
Parameters	Young	Elderly	Young	Elderly
T_{max}† (h)			0.62 (0.32)‡ (0.15 to 1.50)§	1.03 (0.74) (0.25 to 3.00)
C_{max}¶ (ng/mL)			1.04 (0.40) (0.35 to 1.97)	0.90 (0.57) (0.10 to 2.68)
AUC (inf)# (hr•ng/mL)	7.24 (1.57) (4.40 to 9.77)	8.71 (2.02) (4.76 to 13.03)	4.93 (1.24) (2.16 to 7.27)	5.24 (2.27) (0.30 to 10.34)
Half-life (h)	4.56 (1.67) (2.06 to 8.70)	5.61 (1.36) (3.25 to 8.79)	4.74 (1.57) (2.89 to 8.79)	6.56 (1.51) (3.75 to 9.17)
Absolute			69 (16)	61 (25)

Bioavailability (%)			(44 to 113)	(3 to 121)
Volume of Distribution[Þ] (L)	487 (155) (305 to 901)	552 (124) (305 to 737)		
Total Body Clearance (L/h)	99 (23) (70 to 154)	82 (21) (52 to 143)		

*****Young subjects (n = 24) are from 20 to 40 years old and elderly (n = 24) are greater than 65 years of age.
†Time to peak plasma concentration.
‡Mean (1 S.D.)
§(range of observed values)
¶Peak plasma concentration normalized to 1 mg dose.
#Area under the plasma concentration-time curve after a 1 mg dose.
ÞDerived from IV data.

Dose proportionality for butorphanol tartrate nasal solution has been determined at steady state in doses up to 4 mg at 6 hour intervals. Steady state is achieved within 2 days. The mean peak plasma concentration at steady state was 1.8-fold (maximal 3-fold) following a single dose.
The drug is transported across the blood brain and placental barriers and into human milk (see PRECAUTIONS: Nursing Mothers).
Butorphanol is extensively metabolized in the liver. Metabolism is qualitatively and quantitatively similar following intravenous, intramuscular, or nasal administration. Oral bioavailability is only 5 to 17% because of extensive first pass metabolism of butorphanol. The major metabolite of butorphanol is hydroxybutorphanol, while norbutorphanol is produced in small amounts. Both have been detected in plasma following administration of butorphanol, with norbutorphanol present at trace levels at most time points. The elimination half-life of hydroxybutorphanol is about 18 hours and, as a consequence, considerable accumulation (~5-fold) occurs when butorphanol is dosed to steady state (1 mg transnasally q6h for 5 days).
Elimination occurs by urine and fecal excretion. When 3H-labelled butorphanol is administered to normal subjects, most (70 to 80%) of the dose is recovered in the urine, while approximately 15% is recovered in the feces.
About 5% of the dose is recovered in the urine as butorphanol. Forty-nine percent is eliminated in the urine as hydroxybutorphanol. Less than 5% is excreted in the urine as norbutorphanol.
Butorphanol pharmacokinetics in the elderly differ from younger patients (see Table 1). The mean absolute bioavailability of butorphanol tartrate nasal solution in elderly women (48%) was less than that in elderly men (75%), young men (68%), or young women (70%). Elimination half-life is increased in the elderly (6.6 hours as opposed to 4.7 hours in younger subjects).
In renally impaired patients with creatinine clearances < 30 mL/min, the elimination half-life was approximately doubled and the total body clearance was approximately one half (10.5 hours [clearance 150 L/h] compared to 5.8 hours [clearance 260 L/h] in healthy subjects). No effect on C_{max} or T_{max} was observed after a single dose.
After intravenous administration to patients with hepatic impairment, the elimination half-life of butorphanol was approximately tripled and total body clearance was approximately one half (half-life 16.8 hours, clearance 92 L/h) compared to healthy subjects (half-life 4.8 hours, clearance 175 L/h). The exposure of hepatically impaired patients to butorphanol was significantly greater (about 2-fold) than that in healthy subjects.Similar results were seen after nasal administration. No effect on C_{max} or T_{max} was observed after a single intranasal dose.
For further recommendations refer to PRECAUTIONS: Hepatic and Renal Disease, Drug Interactions, and CLINICAL PHARMACOLOGY: Individualization of Dosage.

Clinical Trials
The effectiveness of opioid analgesics varies in different pain syndromes.Studies with butorphanol tartrate nasal solution have been performed in postoperative (general, orthopedic, oral, cesarean section) pain, in postepisiotomy pain, in pain of musculoskeletal origin, and in migraine headache pain (see below).

Use in the Management of Pain:

Postoperative Pain
The analgesic efficacy of butorphanol tartrate nasal solution was evaluated (approximately 35 patients per treatment group) in a general and orthopedic surgery trial. Single doses of butorphanol tartrate nasal solution (1 or 2 mg) and IM meperidine (37.5 or 75 mg) were compared. Analgesia provided by 1 and 2 mg doses of butorphanol tartrate nasal solution was similar to 37.5 and 75 mg meperidine, respectively, with onset of analgesia within 15 minutes and peak analgesic effect within 1 hour. The median duration of pain relief was 2.5 hours with 1 mg butorphanol tartrate nasal solution, 3.5 hours with 2 mg butorphanol tartrate nasal solution and 3.3 hours with either dose of meperidine.

In a postcesarean section trial, butorphanol tartrate nasal solution administered to 35 patients as two 1 mg doses 60 minutes apart was compared with a single 2 mg dose of butorphanol tartrate nasal solution or a single 2 mg IV dose of butorphanol tartrate injection (37 patients each). Onset of analgesia was within 15 minutes for all butorphanol tartrate regimens. Peak analgesic effects of 2 mg

intravenous butorphanol tartrate injection and nasal solution were similar in magnitude. The duration of pain relief provided by both 2 mg butorphanol tartrate nasal solution regimens was approximately 4.5 hours and was greater than intravenous butorphanol tartrate injection (2.6 hours).

Migraine Headache Pain
The analgesic efficacy of two 1 mg doses 1 hour apart of butorphanol tartrate nasal solution in migraine headache pain was compared with a single dose of 10 mg IM methadone (31 and 32 patients, respectively). Significant onset of analgesia occurred within 15 minutes for both butorphanol tartrate nasal solution and IM methadone. Peak analgesic effect occurred at 2 hours for butorphanol tartrate nasal solution and 1.5 hours for methadone. The median duration of pain relief was 6 hours with butorphanol tartrate nasal solution and 4 hours with methadone as judged by the time when approximately half of the patients remedicated.

In two other trials in patients with migraine headache pain, a 2 mg initial dose of butorphanol tartrate nasal solution followed by an additional 1 mg dose 1 hour later (76 patients) was compared with either 75 mg IM meperidine (24 patients) or placebo (72 patients). Onset, peak activity, and duration were similar with both active treatments; however, the incidence of adverse experiences (nausea, vomiting, dizziness) was higher in these two trials with the 2 mg initial dose of butorphanol tartrate nasal solution than in the trial with the 1 mg initial dose.

Individualization of Dosage
Use of butorphanol tartrate nasal solution in geriatric patients, patients with renal impairment, and patients with hepatic impairment requires extra caution (see below and PRECAUTIONS).

The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). If adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given.

The initial dose sequence outlined above may be repeated in 3 to 4 hours as required after the second dose of the sequence.

For the management of severe pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients additional doses should not be given for 3 to 4 hours. The incidence of adverse events is higher with an initial 2 mg dose (see Clinical Trials).

The initial dose sequence in elderly patients and patients with renal or hepatic impairment should be limited to 1 mg followed, if needed, by 1 mg in 90 to 120 minutes. The repeat dose sequence in these patients should be determined by the patient's response rather than at fixed times but will generally be no less than at 6 hour intervals (see PRECAUTIONS).

INDICATIONS AND USAGE
Butorphanol tartrate nasal solution is indicated for the management of pain when the use of an opioid analgesic is appropriate.

CONTRAINDICATIONS
Butorphanol tartrate nasal solution is contraindicated in patients hypersensitive to butorphanol tartrate or the preservative benzethonium chloride.

WARNINGS

Patients Dependent on Narcotics
Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness, and diarrhea.
Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

Drug Abuse and Dependence

Drug Abuse
Butorphanol tartrate, by all routes of administration, has been associated with episodes of abuse. Of the cases received, there were more reports of abuse with the nasal solution formulation than with the injectable formulation.

Physical Dependence, Tolerance, and Withdrawal
Prolonged, continuous use of butorphanol tartrate may result in physical dependence or tolerance (a decrease in response to a given dose). Abrupt cessation of use by patients with physical dependence may result in symptoms of withdrawal.

Note: Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence. (See DRUG ABUSE AND DEPENDENCE.)

PRECAUTIONS

General
Hypotension associated with syncope during the first hour of dosing with butorphanol tartrate nasal solution has been reported rarely, particularly in patients with past history of similar reactions to opioid analgesics. Therefore, patients should be advised to avoid activities with potential risks.

Head Injury and Increased Intracranial Pressure
As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control
Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease
In patients with hepatic or renal impairment, the initial dose sequence of butorphanol tartrate nasal solution should be limited to 1 mg followed, if needed, by 1 mg in 90 to 120 minutes. The repeat dose sequence in these patients should be determined by the patient's response rather than at fixed times but will generally be at intervals of no less than 6 hours (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Individualization of Dosage).

Cardiovascular Effects
Because butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk (see CLINICAL PHARMACOLOGY).
Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Use in Ambulatory Patients
1. Opioid analgesics, including butorphanol, impair the mental and physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Effects such as drowsiness or dizziness can appear, usually within the first hour after dosing. These effects may persist for varying periods of time after dosing. Patients who have taken butorphanol should not drive or operate dangerous machinery for at least 1 hour and until the effects of the drug are no longer present.

2. Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with drugs that affect the central nervous system (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects such as drowsiness, dizziness, and impaired mental function.

3. Butorphanol is one of a class of drugs known to be abused and thus should be handled accordingly (see DRUG ABUSE AND DEPENDENCE).

4. Patients should be instructed on the proper use of butorphanol tartrate nasal solution (see PATIENT INSTRUCTIONS LEAFLET and MEDICATION GUIDE FOR PATIENTS).

Drug Interactions
Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.
In healthy volunteers, the pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol tartrate nasal solution were not affected by the coadministration of a single 6 mg subcutaneous dose of sumatriptan. However, in another study in healthy volunteers, the pharmacokinetics of butorphanol were significantly altered (29% decrease in AUC and 38% decrease in C_{max}) when a 1 mg dose of butorphanol tartrate nasal solution was administered 1 minute after a 20 mg dose of sumatriptan nasal solution. (The two drugs were administered in opposite nostrils.) When butorphanol tartrate nasal solution was administered 30 minutes after the sumatriptan nasal solution, the AUC of butorphanol increased 11% and C_{max} decreased 18%. In neither case were the pharmacokinetics of

sumatriptan affected by coadministration with butorphanol tartrate nasal solution. These results suggest that the analgesic effect of butorphanol tartrate nasal solution may be diminished when it is administered shortly after sumatriptan nasal solution, but by 30 minutes any such reduction in effect should be minimal.
The safety of using butorphanol tartrate nasal solution and IMITREX® (sumatriptan) Nasal Spray during the same episode of migraine has not been established. However, it should be noted that both products are capable of producing transient increases in blood pressure.
The pharmacokinetics of a 1 mg dose of butorphanol administered as butorphanol tartrate nasal solution were not affected by the coadministration of cimetidine (300 mg QID). Conversely, the administration of butorphanol tartrate nasal solution (1 mg butorphanol QID) did not alter the pharmacokinetics of a 300 mg dose of cimetidine.
It is not known if the effects of butorphanol are altered by other concomitant medications that affect hepatic metabolism of drugs (erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.
The fraction of butorphanol tartrate nasal solution absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (oxymetazoline), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated if butorphanol tartrate nasal solution is administered concomitantly with, or immediately following, a nasal vasoconstrictor.
No information is available about the use of butorphanol concurrently with MAO inhibitors.

Information for Patients
(see PRECAUTIONS: Use in Ambulatory Patients, and PATIENT INSTRUCTIONS LEAFLET and MEDICATION GUIDE FOR PATIENTS).

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies were conducted in mice and rats given butorphanol tartrate in the diet up to 60 mg/kg/day (180 mg/m^2 for mice and 354 mg/m^2 for rats). There was no evidence of carcinogenicity in either species in these studies.
Butorphanol was not genotoxic in S. typhimurium or E. coli assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.
Rats treated orally with 160 mg/kg/day (944 mg/m^2) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/m^2) subcutaneous dose.

Pregnancy

Teratogenic Effects

Pregnancy Category C
Reproduction studies in mice, rats, and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. However, pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/m^2) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (360 mg/m^2) and 60 mg/kg/oral (720 mg/m^2) also showed higher incidences of post-implantation loss in rabbits.

There are no adequate and well-controlled studies of butorphanol in pregnant women before 37 weeks of gestation. Butorphanol should be used during pregnancy only if the potential benefit justifies the potential risk to the infant.

Labor and Delivery
Butorphanol tartrate nasal solution is not recommended during labor or delivery because there is no clinical experience with its use in this setting.

Nursing Mothers
Although there is no clinical experience with the use of butorphanol tartrate nasal solution in nursing mothers, it should be assumed that butorphanol will appear in the milk in similar amounts following the nasal route of administration.

Pediatric Use
Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use
Of the approximately 1700 patients treated with butorphanol tartrate nasal solution in clinical studies, 8% were 65 years of age or older and 2% were 75 years or older.
Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65 years (see CLINICAL PHARMACOLOGY: Pharmacokinetics). Elderly patients may be more sensitive to the side effects of butorphanol. In clinical studies of butorphanol tartrate nasal solution, elderly patients had an increased frequency of headache,

dizziness, drowsiness, vertigo, constipation, nausea and/or vomiting, and nasal congestion compared with younger patients. There are insufficient efficacy data for patients ≥ 65 years to determine whether they respond differently from younger patients.
Initially a 1 mg dose of butorphanol tartrate nasal solution should generally be used in geriatric patients and 90 to 120 minutes should elapse before administering a second 1 mg dose, if needed (see CLINICAL PHARMACOLOGY: Individualization of Dosage).
Butorphanol and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

Clinical Trial Experience

A total of 2446 patients were studied in premarketing clinical trials of butorphanol. Approximately half received butorphanol tartrate injection with the remainder receiving butorphanol tartrate nasal solution. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.
The adverse experiences described below are based on data from short-term and long-term clinical trials in patients receiving butorphanol by any route. There has been no attempt to correct for placebo effect or to subtract the frequencies reported by placebo-treated patients in controlled trials.
The most frequently reported adverse experiences across all clinical trials were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with butorphanol tartrate nasal solution only, nasal congestion (13%) and insomnia (11%) were frequently reported.
The following adverse experiences were reported at a frequency of 1% or greater in clinical trials and were considered to be probably related to the use of butorphanol.
Body as a Whole: asthenia/lethargy, headache, sensation of heat.
Cardiovascular: vasodilation, palpitations.
Digestive: anorexia, constipation, dry mouth, nausea and/or vomiting, stomach pain.
Nervous: anxiety, confusion, dizziness, euphoria, floating feeling, insomnia, nervousness, paresthesia, somnolence, tremor.
Respiratory: bronchitis, cough, dyspnea, epistaxis, nasal congestion, nasal irritation, pharyngitis, rhinitis, sinus congestion, sinusitis, upper respiratory infection.
Skin and Appendages: sweating/clammy, pruritus.
Special Senses: blurred vision, ear pain, tinnitus, unpleasant taste.
The following adverse experiences were reported with a frequency of less than 1% in clinical trials and were considered to be probably related to the use of butorphanol.
Cardiovascular: hypotension, syncope.
Nervous: abnormal dreams, agitation, dysphoria, hallucinations, hostility, withdrawal symptoms.
Skin and Appendages: rash/hives.
Urogenital: impaired urination.
The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term butorphanol tartrate nasal solution trials and under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.
Body as a Whole: edema.
Cardiovascular: chest pain, hypertension, tachycardia.
Nervous: depression.
Respiratory: shallow breathing.

Postmarketing Experience

Postmarketing experience with butorphanol tartrate nasal solution has shown an adverse event profile similar to that seen during the premarketing evaluation of butorphanol by all routes of administration. Adverse experiences that were associated with the use of butorphanol tartrate nasal solution and that are not listed above have been chosen for inclusion below because of their seriousness, frequency of reporting, or probable relationship to butorphanol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These adverse experiences include apnea, convulsion, delusion, drug dependence, excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements, overdose, and vertigo.
Reports of butorphanol overdose with a fatal outcome have usually but not always been associated with ingestion of multiple drugs.

DRUG ABUSE AND DEPENDENCE

Butorphanol tartrate nasal solution is listed in Schedule IV of the Controlled Substances Act (CSA).
Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence with butorphanol tartrate. Special care should be exercised in administering butorphanol to patients with a history of drug abuse or to patients receiving the drug on a continuous basis for an extended period.

Clinical Trial Experience
In all clinical trials, less than 1% of patients using butorphanol tartrate nasal solution had experiences that suggested the development of physical dependence or tolerance. Much of this information is based on experience with patients who did not have prolonged continuous exposure to butorphanol tartrate nasal solution. However, in one controlled clinical trial where patients with chronic pain from nonmalignant disease were treated with butorphanol tartrate nasal solution (n = 303) or placebo (n = 99) for up to 6 months, overuse (which may suggest the development of tolerance) was reported in nine (2.9%) patients receiving butorphanol tartrate nasal solution and no patients receiving placebo. Probable withdrawal symptoms were reported in eight (2.6%) patients using butorphanol tartrate nasal solution and no patients receiving placebo in the chronic nonmalignant pain study. Most of these patients abruptly discontinued butorphanol tartrate nasal solution after extended use or high doses. Symptoms suggestive of withdrawal included anxiety, agitation, tremulousness, diarrhea, chills, sweats, insomnia, confusion, incoordination, and hallucinations.

Postmarketing Experience
Butorphanol tartrate has been associated with episodes of abuse and dependence. Of the cases received, there were more reports of abuse with the nasal solution formulation than with the injectable formulation.

OVERDOSAGE

Clinical Manifestations
The clinical manifestations of butorphanol overdose are those of opioid drugs in general. Consequences of overdose vary with the amount of butorphanol ingested and individual response to the effects of opiates. The most serious symptoms are hypoventilation, cardiovascular insufficiency, coma, and death. Butorphanol overdose may be associated with ingestion of multiple drugs (see ADVERSE REACTIONS: Postmarketing Experience).
Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment
The management of suspected butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness, and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.
The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.
In managing cases of suspected butorphanol overdosage, the possibility of multiple drug ingestion should always be considered.

DOSAGE AND ADMINISTRATION
Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly and in patients with hepatic or renal disease requires extra caution (see PRECAUTIONS and CLINICAL PHARMACOLOGY: Individualization of Dosage). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

Use for Pain
The usual recommended dose for initial nasal administration of butorphanol tartrate nasal solution is 1 mg (1 spray in **one** nostril). Adherence to this dose reduces the incidence of drowsiness and dizziness. If adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given.
The initial dose sequence outlined above may be repeated in 3 to 4 hours as required after the second dose of the sequence.
Depending on the severity of the pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients, single additional 2 mg doses should not be given for 3 to 4 hours.

Use in Balanced Anesthesia
The use of butorphanol tartrate nasal solution is not recommended because it has not been studied in induction or maintenance of anesthesia.

Labor
The use of butorphanol tartrate nasal solution is not recommended as it has not been studied in labor.

Safety and Handling
Butorphanol tartrate nasal solution is an open delivery system with increased risk of exposure to health care workers.
In the priming process, a certain amount of butorphanol may be aerosolized; therefore, the pump sprayer should be aimed away from the patient or other people or animals.

The disposal of Schedule IV controlled substances must be consistent with State and Federal Regulations. The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

HOW SUPPLIED

Butorphanol Tartrate Nasal Solution, USP is supplied in a child-resistant vial containing a 2.5 mL bottle of nasal spray solution (10 mg/mL) and a metered dose spray pump with protective clip and dust cover (NDC 0378-9639-43; individual unit). A patient instructions leaflet and medication guide for patients are enclosed. On average, one bottle will deliver 14 to 15 doses if no repriming is necessary.

STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F) [See USP].

Dispense in a tight, light-resistant container as defined in the USP using a child resistant closure.

PHARMACIST ASSEMBLY INSTRUCTIONS FOR BUTORPHANOL TARTRATE NASAL SOLUTION , USP: The pharmacist will assemble Butorphanol Tartrate Nasal Solution, USP prior to dispensing to the patient, according to the following instructions:

1. Open the child-resistant plastic container and remove the spray pump and solution bottle.
2. Assemble Butorphanol Tartrate Nasal Solution, USP by first unscrewing the white cap from the solution bottle and screwing the pump unit tightly onto the bottle. Make sure the clear dust cover is on the pump unit.
3. Return the Butorphanol Tartrate Nasal Solution, USP bottle to the child-resistant plastic container for dispensing to the patient with the patient instructions leaflet and medication guide for patients.

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MEDICATION GUIDE FOR PATIENTS

Butorphanol Tartrate Nasal Solution, USP

CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

What is the most important information I should know about butorphanol tartrate nasal solution?

- **Your doctor has prescribed butorphanol tartrate nasal solution to treat your pain. The medication in butorphanol tartrate nasal solution belongs to a group of medicines that is known to cause dependence and abuse. Butorphanol tartrate nasal solution causes these effects only in a small number of patients. However, because it can have these effects, it is VERY IMPORTANT that you not use butorphanol tartrate nasal solution more often or in larger doses than your doctor has instructed. Also, it is important to have regular checkups with your doctor to ensure that you're using butorphanol tartrate nasal solution correctly. The longer you use butorphanol tartrate nasal solution, the greater your risk of getting dependent on it.**
- **Because butorphanol tartrate nasal solution may make you feel sleepy or dizzy, do not drive or operate dangerous machinery, e.g., automobiles, until you can no longer feel the effects of the drug. Also, do not drink alcohol while using butorphanol tartrate nasal solution because it may worsen any side effects.**

What is butorphanol tartrate nasal solution?

Butorphanol tartrate nasal solution is an opioid narcotic pain reliever that is used for the relief of pain when the use of an opioid pain medication is appropriate. Butorphanol tartrate comes in the form of a nasal spray. One spray of butorphanol tartrate nasal solution is quickly absorbed in the nasal passages.

What do I need to know about using a strong opioid narcotic pain reliever such as butorphanol tartrate nasal solution?

Butorphanol tartrate nasal solution has been reported to be abused. Do not use butorphanol tartrate nasal solution more often or in larger doses than instructed by your doctor. Follow your doctor's instructions exactly and have regular checkups with your doctor when using butorphanol tartrate nasal solution to ensure you are using butorphanol tartrate nasal solution properly.

Who should not take butorphanol tartrate nasal solution?

Butorphanol tartrate nasal solution should not be used if you have ever had an allergic reaction to the active ingredient, butorphanol, or if you are allergic to benzethonium chloride, a preservative in butorphanol tartrate nasal solution. Butorphanol tartrate nasal solution should not be used by patients less than 18 years old. Butorphanol has been found in the breast milk of women who are using butorphanol tartrate nasal solution. Therefore, butorphanol tartrate nasal solution should not be used by patients who are breastfeeding. Patients over the age of 65 years may need less butorphanol tartrate nasal solution than younger patients.

You should not use butorphanol tartrate nasal solution if you are dependent on another narcotic medicine. Dependence is when you need the medicine and you can't perform normally unless you are taking it.

How should I take butorphanol tartrate nasal solution?

Use butorphanol tartrate nasal solution only as directed by your doctor. Never use butorphanol tartrate nasal solution more often or in larger doses than instructed by your doctor. Since you may experience sleepiness or dizziness, use butorphanol tartrate nasal solution in a comfortable location where you can lie down if necessary.

Usual Dosing

If your doctor prescribed a **1 mg** dose of butorphanol tartrate nasal solution for relief of pain:

• Spray **one spray** into **one nostril** – one spray is a **1 mg** dose. This is the most common initial dose.

If prescribed by your doctor, a second spray may be taken **60 to 90 minutes after the first if needed for pain relief.** If instructed by your doctor, the above sequence may be repeated every **3 to 4 hours** as needed for pain relief. If your pain hasn't lessened or it becomes worse, please contact your doctor immediately.

If your doctor prescribed a **2 mg** dose of butorphanol tartrate nasal solution for relief of pain:

• Spray **onespray** into **eachnostril** – two sprays equal a **2 mg** dose. If instructed by your doctor, this dose of butorphanol tartrate nasal solution may be repeated every **3 to 4** hours as needed for pain relief. If your pain hasn't lessened or it becomes worse, please contact your doctor immediately.

If you have liver or kidney disease, you may need to take butorphanol tartrate nasal solution less often or in a lower dose.

Elderly patients may also need to take a lower dose of butorphanol tartrate nasal solution.

Use and Storage of Nasal Spray Unit

Your pharmacist will assemble the nasal spray unit. **However, you must prime the unit before using it the first time and if it has not been used for 48 hours or longer. NOTE:VIALS DO NOT APPEAR "FULL." THEY ARE PREFILLED TO DELIVER ON AVERAGE 14 to 15 ONE (1) MG DOSES.** If you only use butorphanol tartrate nasal solution occasionally and need to re-prime it each time, the vial will deliver an average of 8 to 10 doses of butorphanol tartrate nasal solution. See additional instructions below for priming and using the spray unit.

What should I avoid while taking butorphanol tartrate nasal solution?

- Because butorphanol tartrate nasal solution may make you feel sleepy or dizzy, do not drive or operate dangerous machinery, e.g., automobiles, until you no longer feel the effects of the drug.

- Do not drink alcohol while using butorphanol tartrate nasal solution because it may worsen drowsiness, dizziness and your general ability to function appropriately.

- Some medications cannot be taken with butorphanol tartrate nasal solution because of unwanted side effects. Before you begin using butorphanol tartrate nasal solution, as well as while you are using it, be sure to tell your doctor about any and all other drugs you are taking, including those sold without a prescription (over-the-counter). Do not take any other medicine, including any over-the-counter medicine, unless directed to do so by a doctor who knows you are using butorphanol tartrate nasal solution.

- Because butorphanol tartrate nasal solution may cause harm to an unborn child, tell your doctor if you are pregnant or planning to become pregnant.

- Because small amounts of butorphanol tartrate nasal solution may appear in breast milk, be sure to consult with your doctor if you are nursing an infant.

- Because of butorphanol tartrate nasal solution's potential to cause dependence or abuse, be sure to tell your doctor if you ever had a problem with overuse of drugs or alcohol.

What are the possible side effects of butorphanol tartrate nasal solution?

The type and frequency of side effects experienced by patients taking butorphanol tartrate nasal solution are those commonly seen with opioid narcotic pain relievers. The most frequently reported side effects in studies with butorphanol were drowsiness, dizziness, nausea and/or vomiting. In studies where patients used butorphanol tartrate nasal solution for up to 6 months, nasal congestion and difficulty sleeping were frequently reported. Butorphanol tartrate nasal solution may affect your breathing. This side effect is serious but unlikely if butorphanol tartrate nasal solution is taken as instructed. Notify your doctor immediately if you experience shortness of breath or other difficulty breathing.

Butorphanol tartrate nasal solution may affect your blood pressure or your heart rate.Notify your doctor immediately if you feel lightheaded, have an irregular heartbeat or have headaches that you did not have before you started taking butorphanol tartrate nasal solution.

Side effects other than those listed above have occurred in some patients. For example, the following side effects have been reported rarely, but may be disturbing if they do occur: visual blurring, dysphoria (feeling of sadness, unpleasantness, or discomfort), floating feeling, and hallucinations. Notify your doctor or pharmacist if any side effects persist or become troublesome.

What do I do if someone takes an overdosage of butorphanol tartrate nasal solution?

If you suspect that someone may have taken an overdosage of this medicine, contact your local poison control center or emergency room immediately.

This medication was prescribed for your current condition. Do not use butorphanol tartrate nasal solution for another condition or give the drug to others. Keep butorphanol tartrate nasal solution and all medicines out of the reach of children. Discard any unused portion of the medicine by removing the cap, rinsing the bottle and spray assembly under the water faucet, and disposing the parts in a waste can where children cannot easily get to them.

This summary does not include everything there is to know about butorphanol tartrate nasal solution. Medicines are sometimes prescribed for uses other than those listed. If you have questions or concerns, or want more information about butorphanol tartrate nasal solution, your doctor and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace a careful discussion with your doctor.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1800-FDA-1088.

This has been approved by the U.S. Food and Drug Administration.

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Morgantown, WV 26505
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PATIENT INFORMATION

Take medication as directed by your doctor. For proper use of the nasal spray, read the following instructions carefully.

NOTE: BOTTLES DO NOT APPEAR "FULL." THEY ARE PREFILLED TO DELIVER ON AVERAGE 14-15 ONE (1) MG DOSES. (THE USUAL DOSE IS 1 MG–ONE SPRAY IN ONE NOSTRIL.)

THE UNIT MUST BE PRIMED WITH ONE OR TWO STROKES IF NOT USED FOR 48 HOURS OR LONGER.

Note: With intermittent use requiring repriming before each dose, the 2.5 mL bottle will deliver an average of 8-10 doses of butorphanol tartrate nasal solution.

When not in use, store solution unit in the child-resistant plastic container.

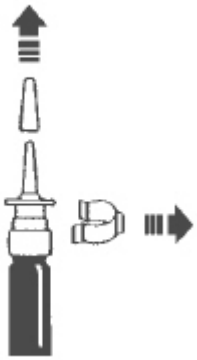
Butorphanol tartrate nasal solution should not be used by anyone other than the person for whom it was prescribed. To prevent this and to reduce the chance of children taking the drug, it is important to dispose of any excess butorphanol tartrate nasal solution just as soon as it is no longer needed.

The best way to safely dispose of the unit is to unscrew the cap, rinse the bottle and spray assembly under the water faucet, and dispose of the parts in a waste can where children cannot easily get to them.

Fig. 1

1. Blow nose gently to clear both nostrils. (Fig. 1)

Fig. 2



2. Pull clear cover off pump unit. Remove protective clip from neck of pump unit. (Fig. 2)

Fig. 3

3. Prime by placing nozzle between first and second finger with thumb on the bottom of bottle. Pump sprayer unit FIRMLY and QUICKLY until a fine spray appears, up to 7-8 strokes. (Fig. 3)

Fig. 4

4. Insert spray tip approximately 1 cm (width of small finger) into one nostril, pointing the tip toward the back of the nose. (Fig. 4)

Fig. 5

5. Close other nostril with your forefinger and tilt your head slightly forward. (Fig. 5)

Fig. 6

6. Pump spray unit firmly and quickly by pushing down on the “finger grips”of the pump unit and against the thumb at the bottom of the bottle. Sniff gently with your mouth closed. (Fig. 6)

Fig. 7

7. After spraying, remove pump unit from nose. Tilt your head backwards and sniff gently a few more seconds. (Fig. 7)

8. Your doctor will tell you whether a two spray dose is needed. If needed, administer a second spray in the other nostril, following steps 4-7. Replace protective clip and clear cover, respectively, (Fig. 2) after each dose.

KEEP OUT OF THE REACH OF CHILDREN.

USUAL DOSE: ONE Spray. Spray ONLY ONCE into ONLY ONE nostril. DO NOT spray into both nostrils unless directed by your doctor. DO NOT repeat sooner than directed by your doctor.

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PRINCIPAL DISPLAY PANEL - 2.5 mL
NDC 0378-9639-43
CIV
2.5 mL
Butorphanol Tartrate
Nasal Solution, USP
10 mg/mLFor Nasal Use Only Rx only
Store at controlled room temperature,
15°-30°C (59°-86°F). [See USP].
See package insert for dosage information
and medication guide.

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